FREQUENTLY ASKED QUESTIONS

Genome-wide analysis identifies 12 loci influencing human reproductive behavior

This FAQ provides accessible answers to some of the basic questions you might have regarding the paper 'Genome-wide analysis identifies 12 loci influencing human reproductive behavior' in the journal *Nature Genetics* doi: 10.1038/ng.3698

If you require further clarification or would like to discuss this research in more detail, please contact: Melinda Mills (melinda.mills@nuffield.ox.ac.uk). Nicola Barban (Nicola.barban@sociology.ox.ac.uk), Harold Snieder (h.snieder@umcg.nl) or Marcel den Hoed (marcel.den_hoed@medsci.uu.se).

Translations of this document are available on: www.sociogenome.com in: Chinese, German, French, Dutch, Swedish and Italian.

A film about this research can be viewed on:
https://www.youtube.com/watch?v=PWSfWSb5KwE

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1. WHAT DO WE STUDY?

What was the central aim of this study?

The aims of this study were to **identify genetic loci** that are related to the **age at first birth (AFB)** and **number of children ever born (NEB)** and **examine their biological function**.

What is 'human reproductive behavior'? How was it measured?

Human reproductive behavior is **defined by two measures**: **age at first birth (AFB)** and **number of children ever born (NEB)**. AFB is the self-reported age when subjects had their first child. In most cases, people were directly asked a question such as: *"How old were you when you had your first child?"* Alternatively, we were able to calculate the measure based on several survey questions (e.g., date of birth of the individual and the date of birth of their first child).

Number of children ever born (NEB) is the self-reported number of children that an individual has. It was often asked directly such as *"How many children do you have?"* We were also able to calculate it based on several survey questions (for example, pregnancy histories and outcomes, number of deliveries). In the majority of cases it was possible to distinguish between biological (live born or stillborn) and adopted or step-children and when this was possible (and for the majority), we focused on the number of live born biological children.

We included cases for the NEB if individuals had likely finished their reproductive career (at least 45 years old for women and 55 for men at the time of study) or in other words, they were highly unlikely to have more children.

Is number of children ever born (NEB) a measure of biological fitness?

Due to improvements in hygiene and the reduction in prenatal, infant and child mortality in industrialized societies, number of children ever born (NEB) has emerged as the gold standard to measure lifetime reproductive success indicating biological fitness. Strictly speaking, fitness is defined not as a value judgement, but rather in scientific studies as the number of children in comparison to the number of children of peers of the same birth cohort. NEB is thus often referred to interchangeably in biological research as life-time reproductive success; number of offspring or as 'fitness' in evolutionary research.

What did we know about the genetic underpinnings of human reproductive behavior before this study?

Previous researchers had largely used twin studies to determine the level or overall amount that genes play in predicting human reproductive behavior, often referred to as 'heritability' or very roughly speaking, the amount of a certain behavior or trait that can be attributed to genetics. Our previous review of this literature[1] showed that the heritability of age at first birth (AFB) is around 25% and for NEB ranges from 15–45%. A recent meta-analysis of 64 reproductive disease traits of women and 25 of men, also found an average heritability of 45% and 36%, respectively. Methods that compare the genetic relatedness of a general population (i.e., not using the twin or family models) showed that 15% of the variance in AFB and 10% of the variance in NEB was associated with common additive genetic variance.[2] Together these results suggested that we should be able to find and locate actual genetic variants associated with human reproductive behavior when conducting GWAS meta-analyses of sufficient sample size.

Both twin and more advanced whole genome techniques determined that there was a genetic component to when we have our first child and how many children we have, but until now were unable to say *which* genes they were or *whether they had a biological function*. What is unique about this study is that it is the first to isolate genetic loci related to age at first birth (AFB) and number of children ever born (NEB) and also examine their biological function.

The majority of research on this topic has also been medical in nature, focusing largely on diseases related to reproduction or menarche and menopause, with no studies examining the genetic underpinnings of reproductive behavior.

Why is it urgent to study the genetic underpinnings of human reproductive behavior now?

In many industrialized societies, contemporary first-time parents are considerably older than decades before, which in turn has consequences for the number of children they can have and their reproductive health. Since the 1970s, there has been a rapid postponement by around 4-6 years in the age at first birth from women having their first child at around 24 years in 1970 to 29 years in 2012 in many industrialized societies.[3] There has not only been postponement, but also significant increases in the levels of childlessness, with around 20-25% of women born from 1965-69 in Southern and Western European countries having no children.[4] The biological ability to conceive a child starts to steeply decline for some women as of age 25, with almost 50% of women being sterile by the age of 40.[5] **This means that a growing number of women start to have their first and subsequent children exactly at the time that their ability to conceive starts to decrease.**

Not surprisingly, this delay has led to an unprecedented growth in infertility (i.e., involuntary childlessness), which impacts between 10-15% of couples in Western countries, with men and women affected equally. An estimated 48 million couples worldwide are infertile, with a large part of it, particularly in men, remaining unexplained.[6] Although therapeutic options for infertility in the form of Assisted Reproductive Technology (ART) are available, they are largely ineffective at older ages. Older mothers also have considerably more problems during gestation and delivery, and older age at pregnancy has been associated with low birth weight and preterm delivery. Birth postponement and a lower number of children has been largely attributed to social, economic and cultural environmental factors (i.e., individual and partner characteristics, socioeconomic status), with virtually no attention paid to the genetic or biological underpinnings of this behavior.[7]

2. HOW DID WE STUDY IT?

The primary analysis that we conducted is called a **Genome-Wide Association Study or GWAS**. Simply put, a GWAS is a search across the entire human genome, examining each genetic locus (or region) one by one to see if there is a relationship (or what we call an association) between our outcomes (AFB, NEB) and a particular genetic locus. These genetic loci contain so-called SNPs (pronounced SNIPs), which refers to single-nucleotide polymorphisms, or in other words, the DNA variants that distinguish us from each other. Humans are 99.9% identical to each other, and it is the 0.1% by which we differ that makes us all genetically unique. A small subset of the 0.1% by which we differ genetically is anticipated to influence reproductive behavior.

In the **largest GWAS on human reproduction to date we combined results from 62 different studies** into what is referred to as a **meta-analysis** with a total sample size of *N*=251,151 for AFB and *N*=343,072 for NEB. We also performed separate meta-analyses for women (AFB, *N*=189,656; NEB, *N*=225,230) and men (AFB, *N*=48,408; NEB, *N*=103,909). We included only individuals of European descent, which is common practice, also since most data are available for such individuals. This reduces the statistical errors that may arise from studying ethnically diverse populations together.

There were **numerous additional techniques and analyses** that we conducted, which are described in detail in the Supplementary Note to our article. We conducted a multi-trait analysis (joint analysis of correlated traits) to boost the statistical power to find genetic loci and measure any pleiotropic[a] architecture underlying AFB and NEB. We also examined sex-specific genetic effects, combined the results from all the SNPs, into a 'polygenic score' (see footnote c), examined genetic correlations with other traits, and examined whether the SNPs we identified matched those previously found for age at menarche and menopause. Some of these results are discussed later in this FAQ document.

In addition to the methods mentioned above, we used the findings generated from the GWAS to **explore the potential biological pathways or functions of the genetic loci that we isolated**. We wanted to go beyond simply finding the location of the genetic loci to determine whether they had any biological function or relevance. We asked whether the genetic loci we found were associated with variants that change the amino acid sequence of the coded protein with a potential deleterious (harmful) effect on function. We also examined which genetic loci influenced gene expression[b], and we examined if the genetic loci we found contain variants on DNA sites that are known to influence the expression of genes, or the binding of proteins, aiming to identify DNA variants and genes that cause the associations we identified in the GWAS. Simply put, we wanted to determine whether the genes we found had a 'function' or in other words were used in the synthesis of a functional protein or in non-protein coding genes (functional RNA). These results are discussed below.

[a] Pleiotropy refers to the case when one gene influences two or more outcomes, such as AFB and NEB. There are, for example, some diseases that affect multiple systems (e.g., phenylketonuria), which are caused by one genetic defect.

[b] Gene expression is the process by which information from a gene is used in the synthesis of a functional gene product. These products are often proteins, but in non-protein coding genes such as transfer RNA (tRNA) or small nuclear RNA (snRNA) genes, the product is functional RNA.

3. WHAT DID WE FIND?

What is the central finding?

The central contribution of this paper is that via our SNP-based meta-analysis (i.e., combined meta-analysis) of GWAS, **we identified 12 independent loci, 10 of which were not previously anticipated to influence reproductive behavior**, that were significantly associated with AFB and/or NEB.

When studied in isolation, individually, each of the SNPs we discovered had an extremely small influence in AFB and NEB. We therefore construct what is termed 'polygenic scores'[c], which includes the information on all contributing genetic factors.

We found **that all 12 genetic loci combined can explain around 1 % of the variability in the average age at which someone has their first baby**.

We **can also predict around 0.2% of the variability of the number of children we will have in the course of our lifetime** using a polygenic score.

Although it may seem low, the results showed that **a 1 standard deviation increase of the NEB polygenic score is associated with a 9% decrease in the probability for women to remain childless** (with no significant effect found for men). Using additional models we also showed that a 1 standard deviation increase in the AFB polygenic score is associated with an 8% reduction in the probability of reproduction at any age in women and 3% in men.

For example, the genetic locus with the strongest association (SNP rs2777888 on Chromosome 3, which consists of DNA letters (or alleles) 'A' or 'G') alone explains around 38 days in the variation of AFB. This means that any additional 'A' one carries in SNP rs2777888 (as opposed to 'G') delays your AFB by 38 days – over a month. If one has the A/A genotype, the effect is a 72 days or a 2.5 month delay in having your first child compared with someone that has the G/G genotype.

For NEB, one of our lead genetic loci (SNP rs10908474 on Chromosome 1) "explains" 0.02 children. Or for instance, if you have the A/A genotype for example, you will on average have 0.04 more children than an individual who has the C/C genotype.

A 1 SD difference in the NEB polygenic score is associated with 0.06 children (Supplementary Table 30,31).

It is vital to note that **we 'explain' some, but very little of the variation in both traits.**

Why are the genetic effects so small?

We have a well-powered study with a trait that has clear physiological mechanisms linking hypothesized genetic networks with our observed outcomes and yet the effects are small in magnitude. Why?

[c] A polygenic score is the sum of trait associated alleles across many genetic loci, typically weighted by effect sizes estimated from a GWAS.

As researchers who have engaged in the study of these human reproductive behavior for decades, we are not surprised, since this type of behavior is complex phenomenon that is not only genetically based. Genetics is only one piece of this larger puzzle and in this study we only examine one type of genetic variant (SNPs) and consider only one of the many possible biological and genetic ways in which individuals may vary. There are also other sources of molecular genetic variation that remain to be discovered and we are currently extending our work further with denser genotyping platforms and other advanced techniques.

Our extension of this work likewise starts to question whether the same genetic factors operate in the same way across different countries and historical periods.[8] In other words – could different genetic variants be more or less important in complex behavior such as human reproduction across different environments?

We are likewise not surprised since previous research on AFB and NEB by social scientists, conducted by ourselves and many experts in the field has consistently demonstrated that socio-environmental conditions are key factors in shaping human reproductive behavior. We know that particularly women's higher educational attainment and attachment to the labor market has resulted in the postponement of entry into parenthood.

Besides expecting small effects from a phenotypic point of view (reproductive behavior), other GWAS studies for complex traits have also consistently identified common variants with small effects, which explain only a small proportion of the trait of interest. This does not impact the biological importance of the findings, as our results have the potential to substantially improve our understanding of human biology. In the context of human disease for example, variants identified by GWAS for diabetes and cardiovascular diseases 'tag' genes that encode well known drug targets for the treatment of such diseases. This implies that a further understanding of the genes underlying the associations we identified for reproductive behavior may someday result in new strategies for infertility and assisted reproductive technology (ART) treatment.

Could these results be used to predict the exact timing of first child and number of children people will have?

No – not at all. As described previously, since each individual SNP or genetic variant has such a small effect, prediction of AFB or NEB using genetic results alone is not possible. Even if we combine the genetic variants together into an index or what is termed a 'polygenic score' using all approximately 9 million SNPs in our data, we can still only predict 0.9% and 0.2% of the variation in AFB and NEB across individuals.

As more and more genetic data becomes available, we anticipate that it will be possible to predict at most 15 to 20% of the variance in AFB and NEB.[2]

It is likewise important to note that even the best 'gold standard' social science predictors of AFB and NEB when entered alone as a single variable in a regression equation also have low predictive power. It is therefore not entirely useful or reductive to only enter one single variable as a predictor without considering additional factors (what we term in multivariate regression as 'controlling' for other factors). In reality, complex outcomes such as AFB and NEB are a culmination of multiple factors such as genetics, parental background, lifestyle,

level of education and national institutional configurations that constrain or enable behavior (e.g., in the case of reproduction it is childcare, work-life reconciliation).

Do the genetic variants that we identified have biological relevance?

We encountered some very exciting biological follow-up findings. **Some of the lead SNPs or genetic loci are related to critical fertility related processes such as: follicle stimulating hormone, estrogen, growth in ovaries, spermatid differentiation, male germ cell development and diseases associated with female infertility (endometriosis, PCOS).**

Via a systematic examination, we examined whether the genetic loci we found had any other reported causal gene function or role (see Table 1 Main Article). Also, using a range of approaches (e.g. gene expression analysis, gene methylation analysis, functional network or enrichment analysis, pathway analysis, regulatory analysis), we identified 24 genes in the 12 GWAS loci that are more likely than neighboring genes to cause the associations identified by GWAS. Some of these genes were previously reported to play a role in fertility-related traits, while others have not yet been subject to study. Relevant pathways and genes include:

- Sperm: spermatid differentiation (*CREB3L4*); spermatid maturation & acrosome reaction (HYAL3); spermatogenesis/testis (*RBM5*; *CYHR1*; *GPT*; *RECQL4*; *PPP1R16A*)
- Fertility in female mice (*EFNA5*)
- Hormones related to fertility (*HCN1*)
- Ovum, oocyte, fallopian tube, prostate (e.g., *MST1R*; *CRTC2*)
- Estrogen responsive gene, sexual maturation, development, (*ESR1*)
- Metabolic endocrine abnormalities, FSH levels (*GPT*)
- Endometriosis (*GATAD2B, ESR1*)
- Polycystic ovary syndrome (*DENND4B)*

Our lead genetic locus on chromosome 3 is associated with methylation and expression of several genes that are known to play a role in sperm function. One lead SNP has been shown to alter the expression of genes *RBM5* and *RBM6*, which have been linked to lower sperm count and lower quality sperm.

Eight genes were prioritized for both AFB and NEB, meaning that such genes influence both reproductive rate and quantum.

This suggests that the genetic loci we identified as being associated with AFB an NEB are not merely driven by behavioral choice, preferences or personality, but can also have an underlying biological function.

Will these findings be useful for researchers who study human reproductive behavior?

Using all the genetic data, including the significant and non-significant SNPs, we created what is called a ‘polygenic score’, which represents our best prediction of each person’s AFB and NEB based on their SNPs. For social scientists we offer something that rarely occurs – we introduce an entirely new variable of a genetic polygenic score to measure AFB and NEB and new way of theoretically thinking about human reproductive choice and behavior. Since

we have empirically determined that there is a genetic component underlying AFB and NEB, this challenges existing behavioral theories that rarely included biology and genetics in their largely choice and preference-based theoretical models and policy interventions. These are, however, not mutually exclusive since genetic factors may also operate through preference, choice and social mechanisms.

We will also make the information openly available and produce a polygenic score for AFB and NEB for all publically available datasets possible, which will allow researchers to include these predictors in their own research.

Are the genetic variants associated with human reproduction associated with other outcomes?

Yes and this is one of the fascinating findings of our research which deserves additional follow-up studies. As shown in Figure 3 (see also Supplementary Note section 7), we examined whether the SNPs associated with AFB and NEB are also associated with 27 related traits that had been discovered in previous GWAS. These included traits for:

- 9 human development and reproduction (age at menarche; age at menopause; age at first sexual intercourse; Tanner stage; voice breaking (boys); birth length and weight; polycystic ovary syndrome; dizygotic twinning)
- 4 behavioural traits (years of education, cigarettes per day, ever smoke, age onset smoking)
- 7 personality & neuropsychiatric traits (neuroticism, openness, schizophrenia, bipolar, subjective well-being, Alzheimer's disease, autism)
- 4 cardiometabolic and obesity related traits (LDL cholesterol, triglycerides, diabetes, fasting insulin level)
- 3 anthropometric traits (height, BMI, waist-hip ratio)

For AFB there was a significant and positive genetic correlation with the human (reproductive) developmental traits of age at menarche, voice breaking in boys, age at menopause, birth weight and age at first sexual intercourse as well as years of education. Conversely, having more alleles related to a later AFB was associated with a lower genetic risk of smoking (ever, number of cigarettes and later onset) and with lower insulin-resistance-related outcomes (BMI, waist-hip ratio adjusted for BMI, fasting insulin, triglyceride levels and risk of diabetes). The link with human development, adiposity and cardiovascular traits suggests a high potential relevance for medical research.

For NEB, age at first sexual intercourse and years of education were the only traits that showed a significant and negative genetic correlation.

Is human reproductive behavior related to other (in)fertility traits?

We tested whether there was a relationship of our polygenic scores for AFB and NEB with other fertility traits and found that a 1 standard deviation increase of the AFB polygenic score is associated with a 3% increase in the age at natural menopause and a 20 day increase in the age at menarche. In other words, those individuals who are genetically endowed to postpone having a first child are also those who have a slightly later age at menarche and menopause. This suggests that individuals with a genetic predisposition to have children later also have an entirely later reproductive window, having later onset of menarche and

menopause. We note, however, that the genetic effects are small on average and those who voluntarily postpone their first birth also do it for many social and institutional reasons.

Are there differences between men and women?

Surprisingly little is known about men's reproduction in comparison with the wide array of studies on women. Having run the GWAS in men and women combined and separately, we were able to compare the effect size of SNPs in the identified genetic loci on AFB and NEB between men and women. While it seems obvious that causal genes that influence sperm differentiation (for example) would only be relevant for men, this observation was not confirmed when comparing the effect size of SNPs in men and women. One reason for this surprising observation could be that genes can have a different function depending on the cell type and tissues. Such genes may thus influence fertility in men and women via currently ill-understood and possibly different mechanisms. We also examined whether there were significant genetic correlations for NEB and AFB between men and women and found that most genetic effects on reproductive behavior resulting from common SNPs are shared by both sexes.

What is the genetic relationship between age at first birth and educational attainment?

The strong relationship between AFB and years of education is not surprising, since educational attainment is associated with a higher AFB and a lower NEB in most advanced societies.[9,10] As discussed previously, the study of the relationship between higher educational attainment and reproduction has been a central focus within demography and related social sciences. The majority of the research demonstrates that achieving higher education (particularly of women) operates to postpone AFB. Other studies have shown that fertility postponement may be related to higher cognitive ability, but additional research is required to separate cognitive scores from social environment (e.g., family environment, social class). Others have found that after controlling for age, physical maturity and mother's education, there is a significant curvilinear relationship with cognitive ability and early sexual intercourse with both very low and very high ability operating as a protective factor against early sexual activity. Further careful research in this area would be necessary to understand the relationship.

4. WHO ARE WE AND WHAT UNITED THIS TRANSDISCIPLINARY TEAM?

Who conducted this study?

This transdisciplinary study united researchers from the social science disciplines of demography, sociology and economics with natural science researchers within genetic epidemiology, molecular genetics, bioinformatics and medical sciences. These unique findings would not have been possible without the integration of experts across the social, natural and medical sciences.

After examining the demographic and social predictors of AFB and NEB, Melinda Mills found it striking that genetic factors had been entirely omitted from the study of human reproductive behavior and choice. Conversely, medical and reproductive genetic experts appeared to ignore the behavioral element of reproductive outcomes. She was awarded a VIDI grant from the Dutch Science Foundation that started in 2011, where she first proposed to conduct this genetic study and began to collaborate with Harold Snieder, a genetic epidemiologist with expertise in conducting GWAS, and later Nicola Barban, Felix Tropf and others joined the project at the University of Groningen (Netherlands). Funding was extended by an ERC Consolidator Grant to Mills in 2013 for the SOCIOGENOME (www.sociogenome.com) project where Mills and co-researchers Barban and Tropf were welcomed by the Sociology Department at the University of Oxford and Nuffield College. Their research was further extended in 2015 with a UK ESRC National Center for Research Methods Grant and more recently extensions to examine infertility by a Wellcome Trust ISSF Grant and John Fell Grant from the University of Oxford. Marcel den Hoed from Uppsala University joined the project as a molecular epidemiologist with experience in post GWAS bioinformatics analyses and translation in 2015. Without this continued generous funding, this research would not have been possible.

After the inception of the project, the authors joined forces with the Social Science Genetic Association Consortium (SSGAC) and received valuable support. SSGAC is a multi-institutional research group that aims to draw statistically rigorous links between genetic variants and social science variables such as behavior, preferences and personality. The SSGAC is organized as a working group of the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE), a successful medical consortium. SSGAC was founded by three social scientists, Daniel Benjamin, David Cesarini and Philipp Koellinger and has an international Advisory Board representing various disciplines. More information about the SSGAC can be found on their website: http://www.thessgac.org/

5. WHAT ARE THE MEDICAL AND SOCIETAL IMPLICATIONS OF THIS STUDY?

In the longer term, this study offers a better understanding of the genetic architecture of human reproductive behavior and its relation to the environment. It likewise has the potential to enable the discovery of predictors of infertility, which would in turn greatly improve family planning but also increase the effectiveness of costly and invasive ART treatments as well as allow couples to realize their fertility intentions. Examination of AFB and NEB may also produce a better understanding of the biology of human reproduction, which in turn may provide insights into fundamental biological mechanisms and could have ramifications for the

study of many health outcomes, especially the etiology of diseases related to the reproductive tract. Furthermore, it is important to understand whether and which proportion of these traits are driven by genetic, behavioral and environmental factors. Relatively little is known about the relationship between indicators of women's reproductive lifespan (menarche, menopause) and reproductive success – or in other words 'How late can you wait?' We anticipate that our study has identified and prioritized several candidates for numerous follow-up experimental studies.

6. ADDITIONAL GENERAL QUESTIONS

How could fertility or childlessness be genetically possible? Wouldn't those who are childless or with fertility problems simply die out over time?

OR, as the scientists ask it: Doesn't Fisher's Fundamental Theorem of Natural Selection state that the genetic variance in fitness should be zero?

A common question is how it could even be possible for those with infertility problems to pass it on to the next generation. Researchers have until now arguably given less attention to NEB than it deserves, perhaps due to a frequent erroneous interpretation of Fisher's Fundamental Theorem of Natural Selection. It has often been misinterpreted to mean that the additive genetic variance in fitness itself should always be close to zero. A close reading of the text shows that Fisher actually argued that fitness is moderately heritable in human populations. The misinterpretation of Fisher's theorem is likely repeated so often due to its intuitive appeal. Naively, it may seem that genes that reduce fitness should have been less frequently passed on, leading to the elimination of genetic variability in traits such as fertility. Nevertheless, we find that fitness traits such as NEB and AFB have significant narrow-sense heritabilities – yet these traits are still not as heritable as morphological traits such as height.

Several reasons have been put forward to explain the persistent genetic variance in fertility. One argument is that new mutations suffice to restore any genetic variance lost to selection. Additional aspects to consider are sexual antagonistic genetic effects, non-additive genetic effects, environment and gene-environment interaction. Sexual antagonism, which is the existence of opposite genotypic effects among sexes, has been often theorized as one of the possible explanations for genetic differences in fertility. In other words, particular genes might influence men and women differently and will therefore still be transmitted to the next generation. Genes that contribute to the fecundability of men may therefore be inherited via women's lineage and those for women via the men's lineage. Certain damaging genetic factors may also only become relevant with age, which arises now with very late fertility.

Is human reproductive behavior nature or nurture?

It is both. Just as complex diseases such as obesity or diabetes are neither purely genetically or socially determined, AFB and NEB are complex outcomes related not only to biological fecundity, but also have a highly behavioral component in that they are driven by the reproductive choice of individuals and their partners, and simultaneously shaped by the social, cultural, economic and historical environment. Genetic factors influence the first two factors of biological fecundity and choice, with the social and historical environment filtering the types of behavior that are possible (e.g., via contraceptive legislation, social norms).

References

Although some scientific references are mentioned in the text, a full explanation and all detailed links to references can be found in the Online Article and Supplementary Note.

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